Potential Chonobiological Triggering Factors of Acute Heart Attack

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Abstract: The immediate triggers of acute heart attack or acute coronary syndrome (ACS) are not known exactly. There is a marked increase in sympathetic activity, neuroendocrino- logical dysfunction, oxidative stress and deficiency of ω3 fatty acids, vitamins, minerals, as well as antioxidants during ACS. Energy intake and expenditure have diurnal variation throughout 24- hour cycle and any disturbance in this cycle may result into disruption of the endogenous clock and neuro-humoral dysfunctions. Clinical studies have reported an increased incidence of reinfarction, sudden death, coronary constriction, myocardial ischaemia, vascular variability disorders and angina, during second quarter of the 24 hour cycle, at the point where there is rapid withdrawal of vagal activity and increase in sympathetic tone. In several studies, among patients with heart attack, there was a significant 2-3 fold increase in cardiac events in the second quarter of the day (6-12 hours) compared to other quarters respectively. Triggers of heart attack were noted in up to 80.0% of patients in various studies. Brain related and psychological mechanisms, i.e., emotional stress, sleep deprivation, cold climate, hot climate, large meals and physical exertion were observed among 30-50% of patients. Such triggers have also been reported in Europe, North America and Asia. These triggering factors are known to enhance sympathetic activity and decrease vagal tone, resulting into increased secretion of plasma cortisol, noradrenaline, aldosterone, angiotensin converting enzyme, interleukin-1, 2, 6, 18 and tumor necrosis factor-alpha, that are proinflammatory. There is also a deficiency in the serum levels of ω3 fatty acids, vitamin A, E, C, coenzyme Q10, magnesium, potassium, melatonin, interleukin-10 (anti-inflammatory) and increase in TBARS, MDA, diene conjugates, TNF-alpha and IL-6, which are indicators of oxidative damage and inflammation, respectively. It is not clear whether the predisposition of ACS is due to size of the meals or other proinflammatory factors of meals.

Keywords: Large meals, breakfast, trans fatty acids, cytokines, lipoproteins, glucose, acute coronary syndrome, myocardial infarction, immediate triggers.

INTRODUCTION

Life on earth is governed by the 24 hour day, and the continuous 24-hour cycle of light and darkness, which may be associated with marked diurnal variations in energy intake and expenditure, throughout this 24-hour cycle [1-3]. Any disturbance in this environmental cycle and/or in the molecular mechanisms that sustain this cycle may add a third dimension to the equation. Apart from these mechanisms, there are seasonal variations in the functioning of the endogenous clock, which may have a role in metabolic responses to seasonal availability of food and the development of obesity, acute coronary syndrome (ACS), stroke and possibly metabolic syndrome in the winters, which may be due to short term adaptation aimed at keeping the organism alive when food was not available during winters in the ancient time [2-7]. The exact mechanism and the immediate triggers of ACS and stroke are not known [2-8]. Clinical manifestations of these attacks also do not occur at random clock times, but according to a time structure [1-7].

Adverse effects of the diet were known to Indians from the ancient times, which is evident from the following verse from an ancient scripture Bhagwatgeeta. "Foods which are bitter, acid, salted, burnt, fried and punjent give rise to pain, mental stress and diseases"(3100BC). Charaka (600BC), a great physician of India, knew about the role of diet and lifestyle in the pathogenesis of heart attack, which would be clear from the following verse: "Heart attack is born by the intake of fatty meals, overeating, excess of sleep, lack of exercise and anxiety". Charaka Sutra, 600BC. While Charaka belonged to a family of mainly preists, Sushruta was from a family of warriors. Charaka was supposed to live

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in Taxila University in north of India and was a Brahman physician, Sushruta was a surgeon from Vishwamitra family from Varanasi. In Mahabharata scripture, he is represented as a son of that royal sage. The garuda puranam scripture places Divodasa as 4th in descent from Dhanavantari, the first propounder of the medical sciences upon earth, whereas the Sushruta samhita describes both as same persons. Sushruta gave a clear description of atheroscerosis or *madroga*: "Excess intake of fatty foods and lack of exercise causes obesity and narrowing of the channels taking blood to the heart. It is useful to use guggul, triphala and silajit (rock deposits) in the treatment".

In the 7th century BC, one Chinese physician proposed that "increased consumption of salt may cause hardening of the pulse". About 2000 years ago from now (1st century), Confucius, the Chinese philosopher taught his students: "the higher the quality of foods, the better, and never rely upon the delicacy of cooking". Thus a dietary guideline based on experience, observation and thinking was given as: "cereals, the basic, fruits the subsidiary, meat the beneficial and vegetable the supplementary". Therefore, the concept of eating, a diet high in animal foods, and preference for meat and greasy foods, possibly rich in ω3 fatty acids, have been shaped over hundreds of years among Chinese, but the total fat intake remained within desirable limits and did not exceed physiological energy needs as in the west. In addition, these dietary patterns were associated with enormous physical activity and sports such as hunting, and also possibly meditation due to introduction of Budhism, possibly posing no significant problem of non-communicable diseases during that period. Moreover, the meat was from running animals with favorable fatty acid composition. It seems that TsimTsoum diet and lifestyle was known to Indians and Chinese from the ancient period. (http://www.tsimtsoum.net/introduction_07.php).

THE EVOLUTION OF TRIGGERS

It is proposed that triggers involved in the development of cardiovascular diseases including ACS, stroke and metabolic syndrome are manifestations of maladptation of certain molecular mechanisms which evolved during scarcity. The ancient man had no food supply in the early morning and in the night, a condition to which they responded by conserving energy during these two periods of the 24-hours cycle. It is also possible that Homo sapiens has adapted his physiological functions to the 24-hours rhythmic environment, enabling him to anticipate predictable daily changes in the environment, therefore optimising the timing of relevant biological processes to this endogenous clock. In turn, this evolutionary adaptation may result into disruption of biochemical environment in our modern body; a large meal as breakfast or dinner may be associated with several adverse effects such as hyperglycemia, hyperinsulinemia, increase in free fatty acids, catecholamines and superoxide anions as well as increase in proinflammatory cytokines which are known to cause endothelial dysfunction and rupture of the unstable plaque, resulting into abnormal circadian rhythms of cardiovascular events in association with other biological and neurohumoral dysfunctions. Homo sapiens and Homo erectus were not storing any food to eat in the morning and in the night, because they were hunting in the morning, and possibly ate heavy lunches. Therefore, increased consumption of energy as breakfast or as dinner may disrupt the functioning of the endogenous master clock [1-13]. It is possible that certain external activities, known as triggers, play a major role in the occurrence of these attacks.

In one study [5], half of all heart attack patients reported a temporal relationship between characteristic activities and occurrence of the ACS. Emotional stress, sleep deprivation, large meals, mild and heavy physical exertion were the most frequently reported triggering factors of ACS, in association with marked reduction in antioxidant vitamins A, E , C, beta-carotene, coenzyme Q10, magnesium, potassium, as well as increase in oxidative stress and proinflammatory cytokines, in various studies [1-7, 11-13]. A large breakfast or dinner may also disturb the endogenous clock, responsible for conservation of energy, during the 2nd and 3rd quarters of the 24-hour cycle, causing obesity. Halberg and coworkers as well as Arble *et al.* provided clinical evidence that eating large dinners may be associated with weight gain, compared to same amount of energy when consumed in the morning [14-18]. It is proposed that the mechanism of conservation of energy by the endogenous clock is greater in the evening compared to morning resulting into weight gain in the night eating syndrome. However, eating a larger breakfast compared to dinner may be more dangerous because the period of 6.00-12.00 hours in the 24 hour cycle appears to be highly vulnerable for endogenous master clock present in the suprachiasmatic nucleus.

THE EVOLUTION OF CIRCADIAN RHYTHM

Homo sapiens adapted to have circadian rhythms of increased release of testosterone in the early morning, which is the most important physiological rhythm of men from ancient time. Because life expectancy of early men was limited, such rhythm was developed to facilitate intercourse and conceive progeny as well as to protect it [1]. Most men were killed during hunting, fall from hill or tree, fighting with wild animals, from snake bite and other accidents. Testosterone is a potent oxidant and sexual activity is associated with increased sympathetic activity in both men and women, which in turn predisposes the endogenous clock to develop circadian increase in sympathetic activity with high levels of catecholamines and decrease in parasympathetic activity with low melatonin during the 6.00-1200 quadrant of the 24 hours cycle.

Singh *et al*. proposed [1] that hunting used to start at about sunrise, causing enormous excitement, physical and mental exertion, and increased sympathetic activity related to the running behind the animals while animals came for drinking water at river banks. Therefore, this period of 7.00 to 11.00 hours in the morning was associated with marked secretion of cortisol, catecholamines, aldosterone, angiotensin and renin in a state of low melatonin, which became a circadian rhythm in modern men. The ancient man was able to adapt and fight the adverse effects of testosterone, cortisol and catecholamines, due to their enormous physical activity, worshiping (meditation), no time for and no availability of breakfast. On the contrary, modern man is not able to resist eating in the morning before exercising although his endogenous clock has adapted to conserve energy during this vulnerable period, resulting into increased rhythmicity of car-

diac events in the second quarter of the day due to greater adverse effects of energy and nutrients.

There appears to be strong evidence for a link between these triggers and the sequences of cellular and pathophysiological events that are postulated responsible for rupture of coronary plaques leading to cardiovascular events. The morning increase in platelet aggregability is a most frequent trigger of ACS, which may be the result of increased secretion of cortisol, aldosterone, catecholamines, angiotensin, free fatty acids, triglycerides [7-11] and decreased vagal tone that are known to be enhanced by feeding and benefited by fasting. Apart from above triggers, presence of risk factors such as low heart rate variability, excess fat, insulin resistance, obesity and pollution may trigger brain-related and other hormonal mechanisms in the development of coronary thrombosis [1]. Both clinical and biochemical factors may be related to a molecular clock present in the brain suprachiasmatic nucleus.

THE TRIGGERS AND THE CIRCADIAN RHYTHM OF CARDIAC EVENTS

Heart attack is a highly dynamic event associated with marked neuroendocrinological dysfunction and heart damage. Studies conducted by various investigators [2-7, 11-13], have demonstrated a marked increase in sympathetic activity, oxidative stress and decrease in parasympathetic activity in association with increase in catecholamines, cortosol, and decrease in melatonin [1] (Table **1**). In one case control study [5], involving 202 patients with ACS, brain related and psychological mechanisms were identified as emotional stress (45.5%), sleep deprivation (27.7%), cold climate (29.2%), hot climate (24.7%), large meals (47.5%) and physical exertion (31.2%). These triggering factors are known to enhance sympathetic activity and decrease vagal tone, resulting into adverse biochemical environment in the body tissues. These observations were further demonstrated in another study [4] involving 54 patients of which 41 patients had acute myocardial infarction and the rest were at first or second stage of heart attack. Age and sex matched control subjects (n=85) were randomly selected from the population of the city of Moradabad drawn from a similar age range of subjects after exclusion of heart attack (n=9), diabetes (n=6) and excess intake of trans fatty acids (n=20). According to that study, a large breakfast was a predisposing factor of cardiac events in the second quarter of the day and it was significantly associated with metabolic reactions. That study also indicated that acute responses of circadian rhythms were important factors in the pathogenesis and complications of heart attacks and that a large breakfast in association with nitrite deficiency may further trigger circadian rhythms. However more studies in a large number of subjects would be necessary to confirm findings. A large meal being a triggering factor for ACS has also been demonstrated by the TRIMM study [6] and the MILIS study [3].

Clinical studies have reported an increased incidence of ACS, sudden death and coronary artery constriction during the first quarter of the day when there is rapid withdrawal of vagal activity and increase in sympathetic tone. According to a case control study [5], among 202 patients of heart attack, a significant ($P<0.02$) increase in cardiac events was observed to occur in the second quarter of the day (6-12hours) compared to other quarters respectively (16.8%, 41.0%, 13.8%, 28.2%). This characteristic remained common in both men and women and among patients with and without known heart attack (n=52), diabetes (n=53) and hypertension (n=75). In another study [4] among 54 patients with ACS, there was a significant greater incidence of cardiovascular events in the second quarter of the day (6.00:AM to 12.00:AM) compared to the thrid quarter. Circadian rhythmicities of cardiovascular events have also been reported in the TRIMM study as well as in the MILIS Study [3, 6].

BIOCHEMICAL MECHANISMS

There is evidence that ACS is associated with increased secretion of plasma cortisol, noradrenaline, aldosterone, angiotension converting enzyme, interleukin(IL)-1,2,6,18 and proinflammatory tumor necrosis factor-alpha [1-7]. IL-18 is one of the most determining factor of rupture of atheroscle-

Table 1. Neuropsychiatric and Other Risk Factors of Acute Coronary Syndrome [5]

Precursors	Healthy Subjects (n-595)	Acute Coronary Sundrome (n=202)
Anxiety	88(14.8)	122(60.4)*
Depression	42(7.0)	45(22.3)*
Type A behaviour	103(17.3)	95(47.2)*
Emotional stress	147(24.2)	92(45.5)*
Sleep deprivation	42(7.0)	56(27.7)*
Cold Climate	-	59(29.2)*
Hot climate (>40 degree celcius)	-	50(24.7)*
Large Meals	147(24.7)	96(47.5)*
Physical Exertion	173(29.1)	63(31.2)*
Diabetes mellitus	70(11.7)	53(26.2)*

rotic plaques along with metalloproteinases and metalloproteases. The ACS is also accompanied by a deficiency in the serum levels of vitamin A, E, C, coenzyme Q, magnesium, potassium, melatonin, interleukin-10 (anti-inflammatory) [4, 5, 12, 13]. In our studies [4, 5, 7], we found a decrease in magnesium, potassium, vitamin A, E, C, beta-carotene and increase in TBARS, MDA, diene-conjugates, TNF-alpha and IL-6, which are indictors of oxidative damage and pro-inflammatory reactions, respectively. Mean lipoprotein(a), total cholesterol and triglycerides were significantly higher whereas mean nitrite level was lower in the ACS group compared to control group [5]. Lp(a), triglycerides, blood glucose, plasma insulin, malondialdehyde, diene-conjugates, TBARS and TNF-alpha and IL-6, which were significantly higher during acute phase, showed a significant decline, whereas serum nitrite and coenzyme Q, an increase, at 4 weeks of follow up, when the acute reactions evoked by ACS were controlled [4].

LARGE MEALS AND ACUTE CORONARY SYNDROMES

There is little information on the role of nutrition on the onset of acute reactions and ACS. Several workers observed that potential triggering factors of acute heart attack could include large breakfast and meals, especially dinner containing high hydrogenated fat, omega-6 fat and refined starches [2-6]. The MILLIS study [3] showed that half of all ACS patients reported a temporal relationship between characteristic activities and the occurrence of ACS. Emotional stress, sleep deprivation, large meals, transition from mild to heavy physical exertion were the most frequently reported triggers of ACS. The Triggers and Mechanisms of Myocardial Infarction (TRIMM) study [6] revealed that 76% of the ACS patients reported an unusual event shortly before the onset of ACS. It is possible that there is a powerful evidence of a link between these triggers and the subsequent biological and clinical events that are postulated to be responsible for ACS. The morning increase in platelet aggregability, heart rate, coronary constriction and oxidative stress and decrease in vagal tone are the most frequent triggers for ACS, which may be the result of increased concentrations of cortisol, catecholamines, aldosterone and angiotensin and decreased concentration of acetylecholine in conjunction with a large breakfast. It is possible that a large meal enhances these markers, predisposing to a cardiac event.

Higher intake of hydrogenated fat, which is known to have adverse effects of lipids and inflammation, was also more common among ACS patients in one study [4] (Table **2**-**4**). It is known that different types of fatty acids and refined carbohydrates in the diet, influence different physiologically relevant mechanisms, especially those concerned with haemostasis and inflammation in the body [19-21]. As the role of various factors, influencing clot formation in the coronary artery and thrombosis, on risk of heart and stroke are more firmly established, our knowledge concerning the effects of different types of nutrients on these factors remains limited.

It is known that postprandial leptin response is lower after a carbohydrate meal in obese women, than in lean controls, suggesting an impairment of such response of leptin regulation due to obesity. Postprandial leptin changes are higher after carbohydrate meal than after a fat meal similar to insulin changes [19-21].

We found that consumption of a large breakfast was associated with greater proinflammatory cytokines, TNF-alpha and IL-6, than in subjects consuming low energy breakfast (Table **3**, **4**). Increased levels of TNF-alpha and IL-6 have been observed in patients with obesity, type 2 diabetes, insulin resistance, glucose intolerance, hypertriglyceridemia, hyperleptinemia and myocardial infarction, which could be greater in patients with ACS. There is no previous evidence that people consuming large breakfast have greater proinflammatory cytokines, as observed in our study. There is potential evidence, however, that ACS may be associated with greater levels of proinflammatory cytokines due to metabolic reactions such as catecholamines, cortisol, serotonin, hyperinsulinemia, hypertriglyceridemia and hypergly-

Table 2. Risk Factors and Other Characteristics of Patients and Control Subjects [4]

	Acute Myocardial Infarction (n=54)	Controls (n=85)
Sex- males	45 (83.3)	76(89.4)
Mean age (years)	49.5± 4.2	52.1± 5.2
Body mass index (kg/m2)	23.7± 3.2	22.4±3.4
Hypertension (>140/90 mmHg)	25(46.3)*	25(29.4)
Glucose intolerance	12(22.2)*	10(11.8)
Diabetes mellitus	14(25.9)	--
Smoking	24(44.4)*	28(32.9)
Higher trans fatty acids (>5g/day)	27(50.0)**	--
Large meals(>1000 Kcal)	27(50.0)**	25(29.4)
Large breakfast(>1000 Kcal)	22(40.7)**	10(11.8)

Values are mean(standard deviation) and number(percentages).*=P <0.05,
** P<0.01; P values were obtained by Student,s t test for continuous variables and by chi square test for ordinal variables.

Table 3. Food Intakes among Patients and Control Subjects [4]

Foods Intake (g/day)	Before Acute Coronary Syndrome (n=54)	Controls (n=85)
Antiatherogenic foods(g/day)		
Wheat,rice and millets	345 ± 43.3*	486 ± 69.6
Roots and tubers	49.5± 4.2	52.1± 5.2
Fruits and vegetables	161 ± 13.2*	221± 25.4
Legumes and pulses	35 ± 6.7*	53± 9.1
Almonds and walnuts	0.5± 0.2*	1.5± 1.2
Fish	10± 5.9*	16.7 ± 6.6
Mustered oil	10± 4.4*	18± 6.9
Proatherogenic foods(g/day)		
Butter, Indian ghee, hydrogenated oils.	38.0 ± 10.0**	16.7 ±5.9
Oils rich in omega-6 fatty acids	22.5 ± 4.7*	11.8 ± 3.5
Total visible fat	70.5 ± 14.6*	46.5 ± 11.7
Sugar, bread, biscuits	208± 57.8**	115± 29.6
Meats(chicken, beef, gote, eggs)	27± 10.7**	40± 12.8
Milk and it products	152 ± 34.6*	112 ± 22.5

Values are mean(standard deviation). *=P <0.05, ** P<0.01; P values were obtained by Student,s t test for continuous variables.

Table 4. Association of Size of Meals with Biochemical Risk Factors of Coronary Syndromes [4]

	Large Breakfast, n=22		Small Breakfast (n=32)
Biochemical data	Baseline	After4 weeks	Baseline After 4 weeks
Triglycerides (mmol/L)	1.88±0.61	1.70±0.38*	1.81+0.60 1.64+0.32*
Blood glucose (mmol/l)	7.7±1.6	6.0±1.2*	6.6+1.4* 5.5+0.30*
Plasma insulin(mg/dl)	47.5+11.3	36.3+5.6**	43.2+8.8* 27.6+3.5*
TBARS(pmol/l)	1.87+0.46	1.32+0.33*	1.77+0.42 1.30+0.31*
Malondialdehyde(pmol/l)	2.68+0.34	2.02+0.21*	2.66+0.33 2.01+0.21*
Diene conjugate(OD)	27.5+4.2	24.6+4.0*	26.2+4.1 24.2+3.5*
Coenzyme Q10(ug/ml)	0.21+0.02	0.32+0.23*	0.23+0.03 0.45+0.24*
Interleukin-6(pg/ml)	32.6+6.2	22.5+4.3*	27.5+5.2* 20.6+0.22*
TNF-alpha(ug/dl)	42.5+12.8	23.6+4.1*	38.2+10.6* 19.6+0.18*
Lipoprotein(a) Ug/ml	23.1±5.4	20.1±4.2*	22.5+4.6 19.7+4.1*

Values are mean standard deviation.*= P<0.05,**=P< 0.01.P values were obtained by analysis of variance by comparison of large breakfast verses small breakfast groups.

cemia that are common in patients with cardiac events. It is possible that people consuming large fatty breakfast enhance the release of catecholamines, glucose, insulin, triglycerides and free fatty acids, which may have an adverse effects on cardiovascular function. However, a few studies just published [14-18] provides added evidence that feeding at the "wrong time" can lead to weight gain. These recent findings on mice were extended to humans in 1973 [17]. A start with nutraceutical indicates that in a person investigated by varying the administration times of coenzyme Q10 (CoQ10), the circadian stage played an important role [14-18]. It is possible that a heavy breakfast as well as a heavy dinner may have adverse effects, particularly when they are rich in hydrogenated fat, ω6 fat and refined carbohydrates.

Experiments in animals (rats) indicate that ventromedial hypothalamic (VMH) lesion in the brain induces hyperphagia and excessive weight gain, fasting hyperglycemia, hyperinsulinemia, hypertriglyceridemia, increase in free fatty acids and glucose intolerance [19-24]. There may be suppressed splenic natural killer cell activity when the animals are hyperphagic and obese [21-24]. There is increased release of interferon-alpha, IL-1, IL-2 and TNF in response to noninflammatory and inflammatory stresses. Long term infusion of norepinephrine plus serotonin into the VMH part of brain impaired pancreatic islet cell function in as much as these abnormalities are observed in insulin resistant animals by several researchers [19-23]. High ω6/ω3 ratio diet can predispose deficiency of ω3 in the ventromedial and lateral hypothalamus causing neuronal damage which may cause increased appetite and hyperphagia leading to intake of large meals at breakfast and dinner. A low ω6/ω3 ratio diet of 1:1 may be protective against hyperphagia. It is possible, that heart attack is associated with high level of psychological and hormonal stress, which may have caused the release of proinflammatory cytokines which becomes worst in presence of ω3 fatty acid deficiency in the tissues. This can damage heart and endothelial cells causing increased susceptibility to atherothrombosis resulting into ACS and heart failure.

EVOLUTION OF DIET AND ADVERSE EFFECTS OF WESTERN DIET

There have been marked changes in the food supply with the development of agriculture over the past 10,000 years. However, only non significant changes occurred in our genes during the past 100 centuries., The spontaneous mutation rate for nuclear DNA is estimated at 0.5% per million years. Hence, over the past 10,000 years there has been time for very little change in our genes, possibly 0.005%. Our genes appear to be similar to the genes of our ancestors during the Paleolithic period 40,000 years ago, the time when our genetic profile was established. Moderm man appears to live in a nutritional environment which completely differs from that for which our genetic constitution was selected. In fact, it is only over the last 100-200 years that dietary intakes have changed significantly, causing increased intake of saturated fatty acids (SFA) and linoleic acid, and decrease intake of ω3 fatty acids, from grain fed cattle, tamed at farm houses, rather than meat from running animals. There is a marked decrease in the intake of vitamins and antioxidants. The food and nutrient intake among hunter-gatherers and during the Paleolithic period are estimated. There is marked reduction in consumption of ω3 fatty acids, vitamins, minerals and proteins, and significant increase in the intakes of carbohydrates (mainly refined), fats (saturated, trans fat, linoleic acid) and salt compared to the Paleolithic period [26].

The Columbus Concept establishes that humans evolved on a diet that was low in saturated fat and the amount of ω3 and ω6 fatty acids was quite equal [26]. Wild-type diets are characterized by balanced ratios (polyunsaturated:saturated = ω6:ω3 = 1:1) as parts of dietary lipid patterns rich in monounsaturated fatty acids (P:M:S = 1:6:1). These ratios represent the overall distribution of fats in a natural untamed environment (www.columbus-concept.com). The Columbus Concept foods include egg, milk, meat, oil, and bread, all rich in ω3 fatty acids, similar to wild foods consumed until 100-200 years ago. Blood lipid composition does reflect one's health status: (a) circulating serum lipoproteins and their ratio provide information on their atherogenicity to blood vessels and (b) circulating plasma fatty acids, such as ω6/ω3 fatty acid ratio, give indication on proinflammatory status of blood vessels; (a) and (b) are phenotype-related and depend on genetic, environmental and developmental factors. As such, they appear as universal markers for holistic health. Blood cholesterol is central to this approach. Its 3D-representation shows how circulating lipoproteins affect blood vessels integrity upon their circulating throughout the body. Of major importance appear the essential dietary nutrients (essential amino acids, fatty acids, antioxidant vitamins and minerals) and the functional components of the regimen (diet, sport, spiritualism, etc). An example is given of an essential dietary nutrient and of a functional component of man's regimen that affect health in a predictive way derived from the 3D-representation of blood cholesterol. The Tsim Tsoum Concept is an extension of the Columbus concept which includes the simultaneous approach of controlling brain-body connection. http://www.tsimtsoum.net/introduction_07.php). Figs. (**1**, **2**).

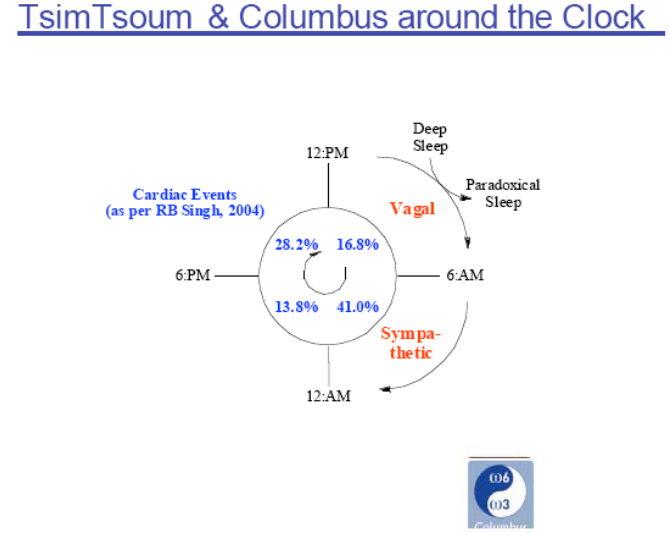

Fig. (1). Circadian Rhythms of ACS, Columbus & TsimTsoum Concepts.

Dietary fat composition can also influence platelet function, platelet aggregation and blood clotting [25, 26]. Recent evidence indicate that dietary butter or coconut increase the sensitivity of platelets to aggregation and clot formation and enhances the release of harmful catecholamines [25]. Hypercholesterolemia is known to be associated with an increased sensitivity of platelets to aggregating agents. A large breakfast rich in fat may enhance platelet aggregation and clotting resulting into heart attack, as noted in our study. Reduction in the saturated fat in the diet may decrease platelet aggregation and catecholamines, resulting into decrease in blood pressure and heart rate. A diet rich in ω3 fatty acids may decrease cytokines and hence may be beneficial because it is cardioprotective as well as neuroprotective [19-39].

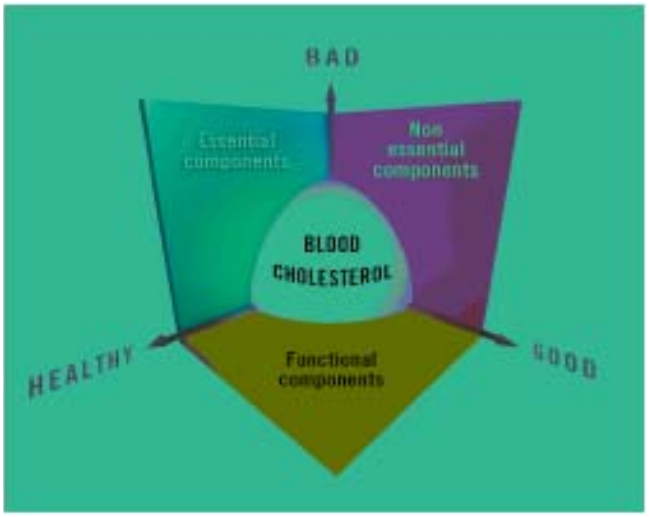

Fig. (2). Blood cholesterol as a Marker for Holistic Health. The Columbus Concept (www.columbus-concept.com) deals with lifestyle's **essential** components to man's health. The TsimTsoum Concept (www.tsimtsoum.net) focuses on lifestyle's **functional** components to human's health. These latter differ from the former components in that they do not contribute to the daily energy intake (DEI = +/- 0) on the one hand, tend to elevate man to human-being on the other hand. They encompass those components that characterize the non-invasive interaction of man's body/mind with his environment through recognition of his evolutionary nature, ie heritage & development.

We have found that subjects eating low energy diet and no breakfast had low blood pressure, lower glucose, insulin, cholesterol, triglycerides and cytokines. In 32 subjects, on no breakfast, fruits and vegetables in the lunch and normal dinner, we observed a very low blood pressure no vascular variability and no overweight and obesity, compared to subjects eating normal meals (unpublished). Sachs *et al.* [33-35] used Dietary Approches to Stop Hypertension (DASH) for decreasing blood pressures, blood lipoproteins and coronary risk. The DASH diet was rich in fruits, vegetables and nuts, similarly rich in ω3 fatty acids and low in ω6 fatty acids to Mediterranean diets. Similar dietary [18-23] interventions have been used by other workers for the last three decades to modulate blood pressure, obesity, diabetes, dyslipidemia and coronary risk in patients with high risk of CAD. These strategies included fruits, vegetables, whole grains and nuts in the dietary pattern which appear to be similar to the Columbus Concept of diet and lifestyle that may be protective due to a favorable fatty acid ratio, composition in antioxidants and slowly absorbed nutrients [26, 36-40]. It is possible that these diets rich in ω3 fatty acids and low in ω6 fatty acids can modulate the endogenous clock present in the brain, causing circadian decrease in blood pressure, release in coronary constriction and favorable modulation of other biochemical risk factors common in the second quarter of 24 hours.

In conclusion, it is possible that no breakfast or small amount of breakfast including slowly absorbed foods such as Columbus Concept foods and small frequent meals including dinner containing protective foods such as almonds, walnuts and black raisins, whole grains bread, legumes, fruits, vegetables and salads, 5-6 times in a day, may have a beneficial effect on the harmful body chemistry that develops during the 2nd and 4th quarters of the day [25-32]. It is suggested that taking small breakfast and dinner and normal lunch and supper may be protective against the adverse effects of foods during circadian rhythms of our body in the prevention of heart attacks. Recent studies also indicate that fasting for few hours is also cardio and neuroprotective.

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